REMARKS

This responds to the Office Action dated March 25, 2011.

Claims 51 and 52 are added. Therefore, claims 2, 4, 8, 9, 28-30, 41, 43-51 and 52 are now pending in this application.

Claims 2 and 43 are amended. In particular, the preambles of claims 2 and 43 recite methods of stimulating an immune response to an antigenic peptide *in vivo*; language relating to stimulation of the immune response is also added at line 12 of claim 2 and at line 14 of claim 43. Support for stimulating an immune response to an antigenic peptide *in vivo*; is present throughout the specification, for example, at page 4, line 22 to page 5, line 21; at page 6, lines 6-24. Claims 2 and 43 no longer recite manipulation of cancer cells and instead relate to contacting a cell with an antigenic peptide and a photosensitizing agent. Support for use of cells in the methods of the application is provided throughout the specification as filed, for example, at page 8, lines 31-34. In addition, claims 2 and 43 also recite that the methods can be performed *ex vivo* and/or *in vivo*, which is supported by the specification, for example, at page 13, lines 6-9.

Applicants submit that no new matter has been added to the application.

New Claims

Claims 51 and 52 are new. Support for the new claims is present throughout the specification, for example, at page 9, lines 21-24. Applicants submit that no new matter has been introduced in the added claims. Additionally, Applicants respectfully submit that the new claims are novel and patentably distinct over the reference currently cited as a basis of rejection, for example, because WO96/07432 fails to mention the use of such antigen presenting cells. The comments below are also applicable to claims 51 and 52. Accordingly, Applicants respectfully request that the Examiner consider and allow the newly added claims.

The Rejection of Claims under § 102

Claims 2, 4, 8, 9, 28-30, 41, 43-49 and 50 have been rejected under 35 U.S.C. §102(b) as allegedly anticipated by WO 96/07432. The Examiner alleges that WO 96/07432 discloses the steps of Applicants' claims and such steps would inherently result in cell surface expression of an antigen.

However, nowhere does WO 96/07432 disclose stimulation of an immune response or movement of a molecule from the cytosol and into the cell membrane. For example, WO 96/07432 utterly fails to disclose the terms "immune," "stimulate," "expression," "presentation," "MHC," "histocompatibility" and "antigen." WO 96/07432 discloses the term "cell membrane" just once in a sentence that would guide those of skill to conclude that molecules do not penetrate cell membranes (page 1, line 5). Nor is there any recognition or disclosure within WO 96/07432 that peptide antigens can or should be presented by cell membranes. Instead, the focus of the WO 96/07432 disclosure is upon internalization of molecules into the cytosol. For example, the title and claim 1 of the WO 96/07432 disclosure expressly state that molecules are introduced into the cytosol. WO 96/07432 also emphasizes release of molecules into the cytosol in several places at page 2, line 16 to page 3, line 8.

WO 96/07432 further discloses that introduced molecules do not move around the cell and through cellular membranes by themselves. According to WO 96/07432, molecules "will be located in endosomes, lysosomes or other cellular compartments" and light treatment is needed to move molecules out of those compartments and into the cytosol (page 2, line 31 to page 3, line 8). WO 96/07432 expressly states: "The majority of molecules do not readily penetrate cell membranes" (page 1, line 5). WO 96/07432 further discloses that extraordinary methods such as microinjection, red blood cell ghost mediated fusion etc. are needed to introduce molecules through the cell membrane and into the cytosol, but these methods are "impractical, time consuming, inefficient or they induce cell death" (page 1, lines 5-12). WO96/07432 also explicitly states at page 2, lines 32-33 that the disclosed method transports molecules into the cytosol of cells "after which the molecules shall be available in the cytosol" – i.e. not on the cell membrane. One of skill in the art would therefore conclude that the methods of WO 96/07432 only move molecules into the cytosol – not back out through the cell milieu and into the cell membrane, where they can be presented as antigens.

Moreover, WO 96/07432 teaches that light treatment is used "to disrupt the endosomal arid lysosomal membranes and release the molecules into the cytosol" (page 2, lines 19-25). Applicants submit that if the cell's organelles are "disrupted" by light treatment, those of skill in the art would conclude that those organelles could not necessarily function to facilitate transport of molecules to the cell membrane. Similarly, as noted in previous responses, the only examples

described by WO 96/07432 result in internalization of toxins into the cytosol, which kill the cells. When cells are dead their organelles do not function to facilitate cell membrane presentation of antigens.

In view of these teachings, no one of skill in the art would recognize that the methods of WO 96/07432 can move molecules to the cell surface. The emphasis upon introduction into the cytosol would guide those of skill in the art to conclude that WO 96/07432 does not provide the conditions or procedures needed for movement of molecules out of the cytosol and to the cell surface of the cell where they will be presented as antigens. Nowhere does WO 96/07432 contemplate or disclose movement of a molecule to the surface of the cell. WO 96/07432 further emphasizes in the Examples that molecules introduced into the cellular cytosol are active in the cytosol (*see, e.g.,* page 8, lines 25-27; page 9, lines 11-13; page 5, lines 15-18). Therefore, the cytosol is the ultimate location for the molecules internalized by the methods WO 96/07432.

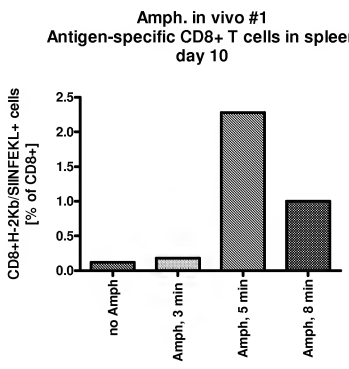
The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). *See also*, MPEP § 2112.

Applicants therefore submit that one of skill in the art would not conclude that WO 96/07432 inherently discloses cell surface expression/presentation of an antigen or stimulation of an immune response by an antigenic peptide.

In addition to failing to disclose presentation on the cell surface, WO 96/07432 fails to enable such presentation. WO 96/07432 especially fails to enable presentation of an antigenic peptide on the surface of a cell by a class I MHC molecule. As described by the Examiner in various Office Actions, including the Office Action dated July 15, 2009, it was not apparent that

photochemical methods would be capable of inducing sufficient MHC class I presentation of an antigen to generate an immune response.

However, Applicants' specification and the accompanying Declaration by Dr. Anders Høgset clearly show that the methods recited in Applicants' claims do so, for example, by employing an antigenic peptide. As described by Dr. Anders Høgset Declaration, antigenic ovalbumin peptides readily stimulated a CD8+ T cell immune response in both spleen cells and blood cells when subjected to the methods recited in Applicants' claims. For example, Figure 7B (reproduced below) shows that mice exhibit a substantial increase in antigen-specific CD8+ T cells after treatment pursuant to the methods of Applicants' claims. The results shown in Figure 7B were generated by co-administering to mice an ovalbumin antigenic peptide and 2.0 μg/ml Amphinex (a solution containing the photosensitizer $TPCS_{2a}$), followed by blue light exposure 20 hours later. The mice were maintained in the dark, sacrificed 10 days later and their spleen cells were analyzed. Figure 7B shows the percent of CD8+ T cells that exhibit specificity for the ovalbumin peptide antigen versus the mouse treatment regimen (i.e., no Amphinex, Amphinex with 3 minutes of light exposure, Amphinex with 5 minutes of light exposure and Amphinex with 8 minutes of light exposure). As illustrated, mice treated by Applicants' methods with both the photosensitizer and 5 minutes light exposure exhibit a 20-fold or greater increase in the percent of antigen-specific CD8+ T cells than mice not receiving the photosensitizer.



In contrast, the WO 96/07432 disclosure fails to disclose anything whatsoever about antigen presentation or the stimulation of an immune response with an antigenic peptide.

Applicants therefore submit that WO 96/07432 fails to enable the subject matter of claims 2, 4, 8, 9, 28-30, 41, 43-51 and 52, and also fails to inherently disclose this subject matter.

Withdrawal of this rejection of claims 2, 4, 8, 9, 28-30, 41, 43-51 and 52 under 35 U.S.C. §102(b), is respectfully requested.

The Rejection of Claims under § 112

Claims 2, 4, 8, 9, 28-30, 41, 43-49 and 50 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. The Examiner has raised two issues under 35 U.S.C. §112, second paragraph, which Applicants submit have been obviated by the clarifying amendments to claims 2 and 43.

Withdrawal of this rejection under 35 U.S.C. §112, second paragraph, is respectfully requested.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicants' representative at (516) 795-6820 to facilitate prosecution of this application.

If necessary, please charge any additional fees or deficiencies, or credit any overpayments to Deposit Account No. 19-0743.

Respectfully submitted,

SCHWEGMAN, LUNDBERG & WOESSNER, P.A.
P.O. Box 2938
Minneapolis, MN 55402--0938
(516) 795-6820

Date Sep. 21, 2011

By / Robin A. Chadwick /
Robin A. Chadwick
Reg. No. 36,477